



SEP 21 2004

Beth Rosenshein  
15149 SE 48th Dr.  
Bellevue, WA 98006

Re: Docket No. 2003P-0357/CP1

Dear Ms. Rosenshein:

This letter responds to your citizen petition dated August 1, 2003 (Petition). You request that the Food and Drug Administration (FDA) make the following two changes to the labeling for Premarin (conjugated estrogens) tablets:

- Update the drug/laboratory test interactions section of the prescribing information to recognize the decreased levels of testosterone with oral estrogen use.
- List all known active components of Premarin in the description section of the prescribing information.

FDA has considered the information submitted in your petition and addresses your requests in this response. For the reasons explained below, your petition is granted in part and denied in part.

## I. DISCUSSION

### A. Drug/Laboratory Testing Interactions Section of the Labeling

You request that the drug/laboratory test interactions section of the prescribing information for all strengths of Premarin tablets recognize the decreased levels of testosterone with oral estrogen use (Petition at 1, 4). You suggest the following wording: "Free or biologically active hormone levels, i.e., testosterone, are reduced."

The Center for Drug Evaluation and Research's (CDER's) draft *Labeling Guidance for Noncontraceptive Estrogen Drug Products for the Treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms -- Prescribing Information for Health Care Providers and Patient Labeling* (the draft labeling guidance) describes recommended prescribing information for estrogen drug products that treat moderate to severe vasomotor symptoms and/or moderate to severe symptoms of vulvar vaginal atrophy for new drug applications. It also provides labeling recommendations for the patient information leaflet. CDER first issued a draft of the estrogen labeling guidance in

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September 1999 (64 FR 52100). However, on September 10, 2002, CDER withdrew the draft guidance (67 FR 57432), pending consideration of the results from the National Institutes of Health (NIH) Women's Health Initiative.<sup>1</sup> A second draft of this guidance was issued on February 3, 2002 (68 FR 5300). CDER issued a third draft of this guidance on February 17, 2004 (69 FR 7492) (available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>).

The revised draft labeling guidance recommends on page 15 that the following statement be added to the drug/laboratory test interactions section: "Free hormone concentrations may be decreased." As with all draft guidances, we have invited public comments on this document.

We believe this recommended change to the drug/laboratory test interactions section of the labeling for non-contraceptive estrogen products, including Premarin, responds to your request. Therefore, your request concerning recognition of decreased levels of free testosterone is effectively granted.

#### **B. Description Section of the Labeling**

You request that all known active components of Premarin be listed in the description section of the prescribing information in the labeling for Premarin, and you list specific ingredients you would include as active components (Petition at 1, 6).

The current labeling for Premarin appropriately states the drug product's active ingredients. The description section of the Premarin labeling complies with the current U.S. Pharmacopeia (USP) monograph description of conjugated estrogens tablets. The current USP monograph for conjugated estrogens lists sodium equilin sulfate and sodium estrone sulfate as the two major active ingredients. The current USP monograph for conjugated estrogens tablets defines conjugated estrogens tablets in terms of the total of sodium estrone sulfate and sodium equilin sulfate. The patient package insert for Premarin tablets lists these two active ingredients and therefore complies with the current USP monograph.

In 1997, CDER concluded that Premarin is not adequately characterized and that investigations designed to produce the scientific data needed to further determine active ingredients in Premarin are feasible (see May 5, 1997, memo from Director, CDER, to Director, Office of Generic Drugs (the May 5 memo), available at [www.fda.gov/cder/regulatory/initiatives/cestrogens](http://www.fda.gov/cder/regulatory/initiatives/cestrogens)). CDER's Division of Testing and Applied Analytical Development has been working both on its own and in cooperation with Wyeth Pharmaceuticals (the current name of the manufacturer of Premarin) to better characterize Premarin. If these characterization efforts indicate changes to the monographs would be appropriate, CDER may recommend changes to the USP monographs.

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<sup>1</sup> The results of the NIH Women's Health Initiative trial were reported in the *Journal of the American Medical Association*, 2002; 288:321-333.

In support of your request, you state that a citizen petition submitted by Wyeth-Ayerst Laboratories (Docket No. 94P-0429/CP1), requesting that delta 8,9 dehydroestrone (DHES) be listed as an active ingredient of Premarin (Petition at 6), has not been acted upon. Wyeth withdrew this petition on September 9, 2002 (a copy of the withdrawal letter is available on the Internet at <http://www.fda.gov/ohrms/dockets/dailys/02/Sep02/091602/80027b15.pdf>).<sup>2</sup>

Because the Premarin labeling complies with the current USP monograph in identifying the active ingredients, your request to modify the labeling to list other components as active ingredients is denied. If other active ingredients are identified during the process of characterization, we will recommend appropriate changes to the USP monographs for conjugated estrogens and conjugated estrogens tablets and corresponding updates to the labeling.

## II. CONCLUSION

Your request that the drug/laboratory test interaction section of the labeling for Premarin be modified is effectively granted. Your request that the description section of the labeling for Premarin be modified is denied. Therefore, for the reasons discussed above, your petition is granted in part and denied in part.

Sincerely,



Steven K. Galson, M.D., M.P.H.  
Acting Director  
Center for Drug Evaluation and Research

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<sup>2</sup> For a discussion of CDER's position on DHES, see pages 27-31 of the May 5 memo.